09720017

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
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NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	Jun 03	New e-mail delivery for search results now available
NEWS 20	Jun 10	MEDLINE Reload
NEWS 21	Jun 10	PCTFULL has been reloaded
NEWS 22	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 23	Jul 19	NTIS to be reloaded July 28, 2002
NEWS 24	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 25	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 26	Jul 30	NETFIRST to be removed from STN

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 09:38:43 ON 05 AUG 2002

=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:38:52 ON 05 AUG 2002
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STRUCTURE FILE UPDATES: 4 AUG 2002 HIGHEST RN 442512-16-5
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TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

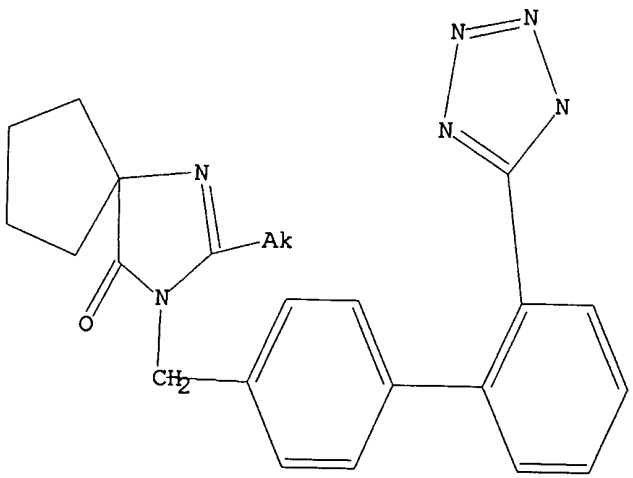
Crossover limits have been increased. See HELP CROSSOVER for details.

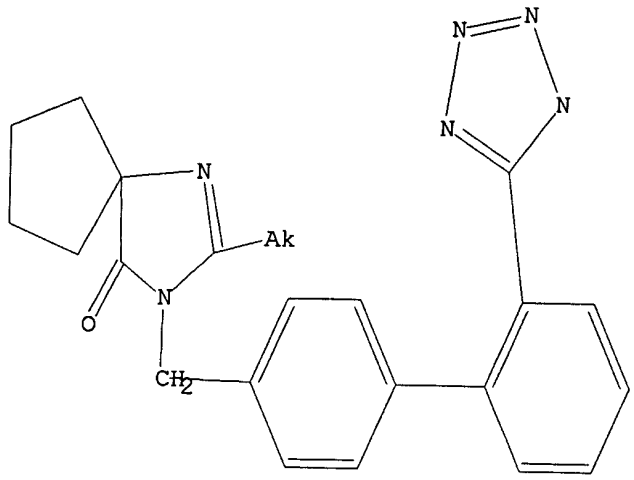
Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09720017.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR





Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 09:39:27 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      3 TO ITERATE

100.0% PROCESSED       3 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             3 TO      163
PROJECTED ANSWERS:                0 TO        0

L2             0 SEA SSS SAM L1

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FULL SEARCH INITIATED 09:39:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     70 TO ITERATE

100.0% PROCESSED      70 ITERATIONS                               20 ANSWERS
SEARCH TIME: 00.00.01

L3            20 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     140.28     140.49

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FILE COVERS 1907 - 5 Aug 2002 VOL 137 ISS 6
FILE LAST UPDATED: 4 Aug 2002 (20020804/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l3 full
L4 294 L3

=> s l4 and crystal?
1409396 CRYSTAL?
L5 6 L4 AND CRYSTAL?

=> d l5 1-6 ibib abs hitstr

L5 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:798026 CAPLUS
DOCUMENT NUMBER: 135:348884
TITLE: Taste masking coating composition based on methacrylate polymer and cellulose ester
INVENTOR(S): Corbo, Michael; Desai, Jatin; Patell, Mahesh; Warrick, Ronald
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080826	A2	20011101	WO 2001-US12709	20010418
WO 2001080826	A3	20020321		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-557924 A 20000420

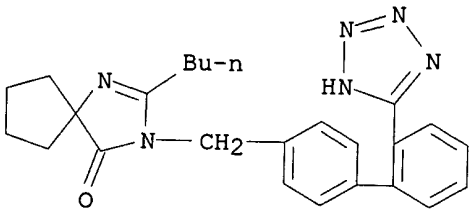
AB There is provided a coating compn. that masks the undesirable taste of a pharmaceutically active ingredient, i.e. drug or medicine, that is taken orally. The coating compn. has a dimethylaminoethyl methacrylate and neutral methacrylic acid ester, a cellulose ester polymer, and an alk.

modifier, e.g, triethanolamine. For example, acetaminophen in the cryst. form having a mesh size about 40 to 80, was coated with a coating compn. of 60% cellulose acetate/28% Eudragit E 100/12% triethanolamine. The same coating compn. was applied as a coating for granular caffeine that was also about 40 to 80 mesh size. The coating thickness was varied and the coated **crystals** and granules were formed into tablets.

IT **138402-11-6**, Irbesartan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(taste masking coatings for oral compns. based on blend of methacrylate polymer and cellulose esters)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	C2	20020516		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

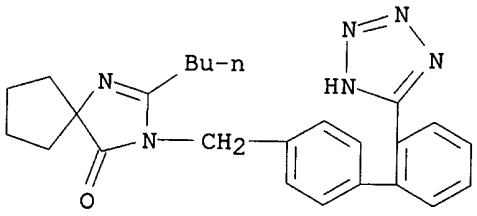
AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of

multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:755340 CAPLUS

DOCUMENT NUMBER: 130:167981

TITLE: A computational approach to intermolecular proton transfer in the solid state: assistance by proton acceptor molecules

AUTHOR(S): Alkorta, Ibon; Rozas, Isabel; Elguero, Jose

CORPORATE SOURCE: CSIC, Instituto de Quimica Medica, Madrid, E-28006, Spain

SOURCE: Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1998), (12), 2671-2676
CODEN: JCPKBH; ISSN: 0300-9580

PUBLISHER: Royal Society of Chemistry

DOCUMENT TYPE: Journal

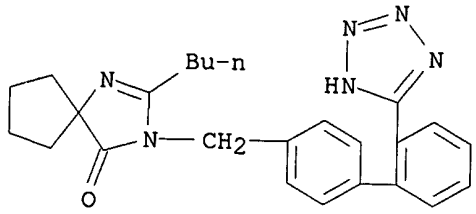
LANGUAGE: English

AB Ab initio (B3LYP/6-311++G**) calcns. were carried out on the proton transfer of 2H-tetrazole and 5-phenyl-2H-tetrazole with and without the assistance of different N bases (H cyanide, NH3 and imidazole). In the absence of base, the proton transfer barrier amts. to 210 kJ mol-1 while in the presence of NH3 it is lowered to 119 kJ mol-1. Also, the inclusion of a solvent cavity of the Onsager type, which increases the 1st barrier, decreases the 2nd one to 67 kJ mol-1 (for .epsilon. = 5) which is consistent with exptl. data for irbesartan (a 5-aryl-2H-tetrazole deriv.).

IT **138402-11-6**, Irbesartan
RL: PEP (Physical, engineering or chemical process); RCT (Reactant); PROC

(Process); RACT (Reactant or reagent)
(2H-tetrazole tautomer; assistance by proton acceptor mols. and d. functional theory calcn. of intermol. proton transfer in solid state)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



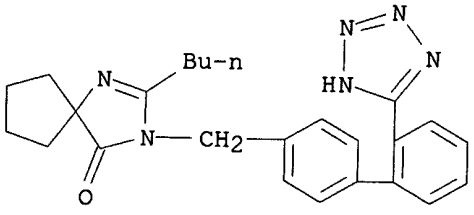
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:451409 CAPLUS
DOCUMENT NUMBER: 129:74251
TITLE: Irbesartan **crystal** form B
AUTHOR(S): Bocskei, Zsolt; Simon, Kalman; Rao, Renee; Caron, Antoine; Rodger, Charles A.; Bauer, Michel
CORPORATE SOURCE: Dep. Chemical Res., Chinoin Pharmaceuticals, Budapest, 1325, Hung.
SOURCE: Acta Crystallographica, Section C: Crystal Structure Communications (1998), C54(6), 808-810
CODEN: ACSCEE; ISSN: 0108-2701
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irbesartan (2-butyl-3-{[2'-(2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-diaaspiro[4.4]non-1-en-4-one, C25H28-N6O), a highly selective angiotensin II receptor (AT1) antagonist was found to exist in two distinct **crystal** forms (A and B). This paper describes the **crystal** structure of irbesartan form B. **Crystallog**. data are given.

IT **138402-11-6**, Irbesartan
RL: PRP (Properties)
(**crystal** structure of polymorph B of)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



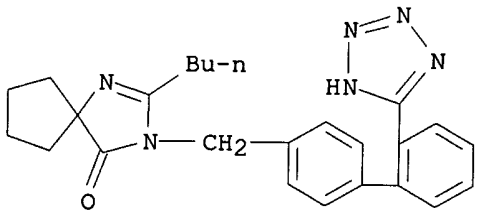
L5 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2002 ACS

09720017

ACCESSION NUMBER: 1998:117711 CAPLUS
DOCUMENT NUMBER: 128:229939
TITLE: NMR study of desmotropy in Irbesartan, a tetrazole-containing pharmaceutical compound
AUTHOR(S): Bauer, Michel; Harris, Robin K.; Rao, Renee C.; Apperley, David C.; Rodger, Charles A.
CORPORATE SOURCE: Sanofi Recherche, International Analytical Department, Toulouse Cedex, 31036, Fr.
SOURCE: Journal of the Chemical Society, Perkin Transactions 2: Physical Organic Chemistry (1998), (3), 475-482
CODEN: JCPKBH; ISSN: 0300-9580
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irbesartan, a novel anti-hypertensive agent (Angiotensin II antagonist), has been found to exist in two **crystal** forms. The soln.-state structure and the solid-state structure of the two forms, designated Form A and Form B, have been probed using a series of NMR methods and correlated with single-**crystal** X-ray results for Form B. The prototropic tautomerism generally exhibited by tetrazole ring systems has been probed using solid-state NMR and it is seen that irbesartan offers a rare example of desmotropic behavior, whereby the isolated **crystal** forms are stable in the solid state yet related through a tautomeric equil. in the soln. state. Nitrogen-15 solid-state CPMAS data have been used to understand the structures of the stable irbesartan **crystal** forms. Form B is shown to undergo an exchange process involving the tetrazole ring. Two-dimensional EXSY 15N spectra are used to understand this process, which involves simultaneous proton-hopping and internal rotation.

IT **138402-11-6**, Irbesartan
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(NMR study of desmotropy in tetrazole-contg. pharmaceutical compd.)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:379664 CAPLUS
DOCUMENT NUMBER: 125:58517
TITLE: Preparation and formulation of a new **crystalline** form of irbesartan
INVENTOR(S): Caron, Antoine; Chantreux, Dominique; Bouloumie, Colette
PATENT ASSIGNEE(S): Sanofi, Fr.
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

09720017

LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 708103	A1	19960424	EP 1995-402322	19951018
EP 708103	B1	20010103		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2725987	A1	19960426	FR 1994-12459	19941019
FR 2725987	B1	19970110		
CA 2160725	AA	19960420	CA 1995-2160725	19951017
US 5629331	A	19970513	US 1995-544027	19951017
CZ 288629	B6	20010815	CZ 1995-2710	19951017
NO 9504154	A	19960422	NO 1995-4154	19951018
CN 1128261	A	19960807	CN 1995-118711	19951018
CN 1061656	B	20010207		
RU 2144536	C1	20000120	RU 1995-118109	19951018
AT 198478	E	20010115	AT 1995-402322	19951018
ES 2155115	T3	20010501	ES 1995-402322	19951018
FI 9504992	A	19960420	FI 1995-4992	19951019
AU 9534335	A1	19960502	AU 1995-34335	19951019
AU 698041	B2	19981022		
ZA 9508850	A	19960527	ZA 1995-8850	19951019
HU 73179	A2	19960628	HU 1995-3016	19951019
JP 08208642	A2	19960813	JP 1995-271512	19951019
IL 115688	A1	19990922	IL 1995-115688	19951019
CZ 288624	B6	20010815	CZ 2000-2544	20000707

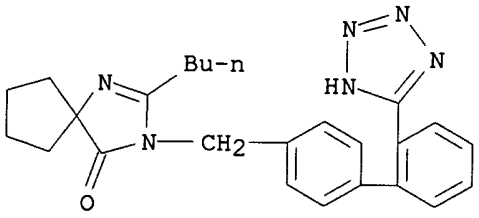
PRIORITY APPLN. INFO.: FR 1994-12459 A 19941019

AB The title compd., 2-butyl-3-[(2'-tetrazol-5-ylbiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one, was prepd. in a new cryst. form by treating 2-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one with an alk. azide in an aprotic polar solvent, neutralizing the salt in an aq. medium, and crystn. from a water-miscible solvent contg. >.apprx.10vol.% water.

IT **138402-11-6P**
RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and formulation of a new cryst. form of irbesartan)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



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NEWS 25	Jul 29	Enhanced polymer searching in REGISTRY
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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:31:47 ON 05 AUG 2002

=> eg
EG IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:31:54 ON 05 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 4 AUG 2002 HIGHEST RN 442512-16-5
DICTIONARY FILE UPDATES: 4 AUG 2002 HIGHEST RN 442512-16-5

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

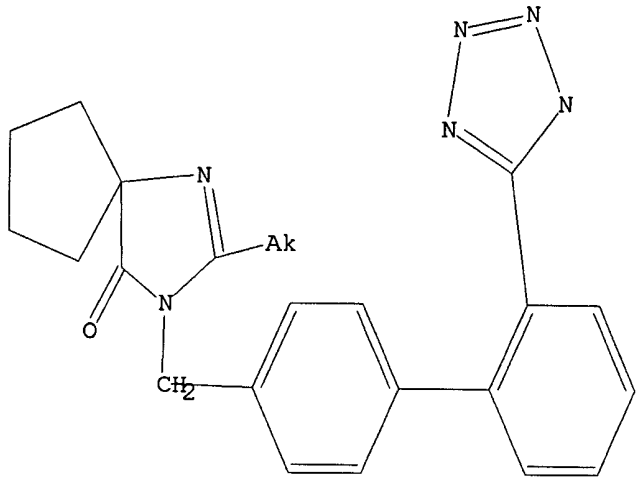
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09720017.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

```
=> s l1 sss sam
SAMPLE SEARCH INITIATED 09:32:17 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      3 TO ITERATE

100.0% PROCESSED       3 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            3 TO      163
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 09:32:22 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     70 TO ITERATE

100.0% PROCESSED      70 ITERATIONS                               20 ANSWERS
SEARCH TIME: 00.00.01

L3           20 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   140.28     140.49

FILE 'CAPLUS' ENTERED AT 09:32:26 ON 05 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 5 Aug 2002 VOL 137 ISS 6
FILE LAST UPDATED: 4 Aug 2002 (20020804/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

```
=> s l3 full
L4          294 L3

=> s l4 and disease?
         614970 DISEASE?
L5          114 L4 AND DISEASE?

=> s l4 and cardiovascular?
          51793 CARDIOVASCULAR?
L6           45 L4 AND CARDIOVASCULAR?

=> s l4 and glaucoma?
           4239 GLAUCOMA?
L7            2 L4 AND GLAUCOMA?

=> s l5 and cardiovascular?
          51793 CARDIOVASCULAR?
L8           36 L5 AND CARDIOVASCULAR?

=> s l5 and hypertension?
          56740 HYPERTENSION?
L9           37 L5 AND HYPERTENSION?

=> s l8 and hypertension?
          56740 HYPERTENSION?
L10          15 L8 AND HYPERTENSION?

=> d l10 1-15 ibib abs hitstr

L10  ANSWER 1 OF 15  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:106875  CAPLUS
DOCUMENT NUMBER:          137:15596
TITLE:                    Inhibition of the renin-angiotensin system ameliorates
                          genetically determined hyperinsulinemia
AUTHOR(S):                Ortlepp, J. R.; Breuer, J.; Eitner, F.; Kluge, K.;
                          Kluge, R.; Floege, J.; Hollweg, G.; Hanrath, P.;
                          Joost, H.-G.
CORPORATE SOURCE:         Medical Clinic I, University Hospital of Aachen,
                          Aachen, 52057, Germany
SOURCE:                   European Journal of Pharmacology (2002), 436(1-2),
                          145-150
                          CODEN: EJPHAZ; ISSN: 0014-2999
```

09720017

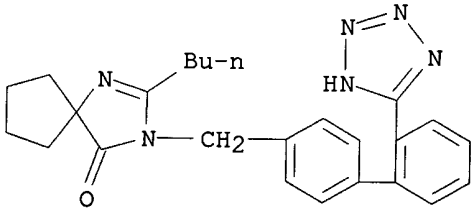
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study was performed to assess the potentially different effects of the angiotensin-converting enzyme inhibitor captopril and of the angiotensin II receptor antagonist irbesartan on the metabolic syndrome in an animal model. Male NZO/BL6 F1 mice were treated with captopril, irbesartan, or placebo for 10 mo: Control animals treated with placebo developed a metabolic syndrome with obesity (55.5.+-.6.3 g), **hypertension** (146.+-.10 mm Hg), hyperinsulinemia (7.2.+-.5.7 ng/mL), hypercholesterolemia (5.1.+-.0.7 mmol/l), cardiac hypertrophy (269.+-.44 mg) and atherosclerotic plaques in the ascending aorta (3.6.+-.1.5 .mu.m2). Treatment with angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist significantly ($p<0.001$) reduces **hypertension** (73.+-.5 and 78.+-.11 mm Hg), cardiac hypertrophy (203.+-.26 and 202.+-.18 mg) and atherosclerosis (2.2.+-.0.9 and 1.8.+-.0.8 .mu.m2). In addn., they prevented the development of obesity (42.2.+-.3.5 and 38.3.+-.2.8 g) and hyperinsulinemia (3.6.+-.1.5 and 1.8.+-.0.4 ng/mL). In conclusion, long-term treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist can ameliorate obesity and hyperinsulinemia in a genetically detd. mouse model.

IT **138402-11-6**, Irbesartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of the renin-angiotensin system ameliorates genetically detd. hyperinsulinemia)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:886157 CAPLUS
DOCUMENT NUMBER: 136:11105
TITLE: Cobalamin compounds useful as **cardiovascular** agents and as imaging agents
INVENTOR(S): Collins, Douglas A.; Hogenkamp, Henricus P. C.
PATENT ASSIGNEE(S): Mayo Foundation for Medical Education and Research, USA; Regents of the University of Minnesota
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001092283	A2	20011206	WO 2001-US17694	20010531
WO 2001092283	A3	20020704		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002049155	A1	20020425	US 2001-873142	20010531

PRIORITY APPLN. INFO.: US 2000-208140P P 20000531
US 2001-267782P P 20010209

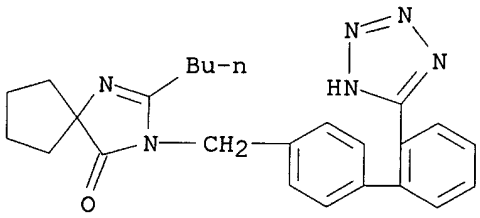
OTHER SOURCE(S): MARPAT 136:11105

AB The invention provides cobalamin derivs. linked to a **cardiovascular** agent, as well as pharmaceutical compns. comprising the compds. and methods for using the compds. in treatment or diagnosis of a **cardiovascular disease**.

IT **138402-11-6D**, Avapro, cobalamin conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cobalamin compds. useful as **cardiovascular** agents and as imaging agents)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:747597 CAPLUS
DOCUMENT NUMBER: 135:267248
TITLE: Vasopeptidase inhibitors, alone or with other agents, for the treatment of isolated systolic **hypertension**
INVENTOR(S): Reeves, Richard A.; Wolf, Robert A.; Chang, Paul I.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074348	A2	20011011	WO 2001-US8240	20010315

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

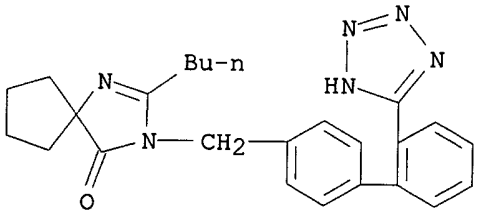
CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002004500 A1 20020110 US 2001-819549 20010328
PRIORITY APPLN. INFO.: US 2000-194499P P 20000403

AB Vasopeptidase inhibitors, esp. omapatrilat, are useful in treating isolated systolic **hypertension**. The vasopeptidase inhibitor may be used in combination with other pharmaceutically active agents.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vasopeptidase inhibitors, alone or with other agents, for treatment of isolated systolic **hypertension**)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:430930 CAPLUS
DOCUMENT NUMBER: 135:162322
TITLE: Regression of left ventricular hypertrophy in human **hypertension** with irbesartan
AUTHOR(S): Malmqvist, Karin; Kahan, Thomas; Edner, Magnus; Held, Claes; Hagg, Anders; Lind, Lars; Muller-Brunotte, Richard; Nystrom, Fredrik; Ohman, K. Peter; Osbakken, Mary D.; Ostergren, Jan
CORPORATE SOURCE: Investigators, Division of Internal Medicine, Karolinska Institutet Danderyd Hospital, Danderyd, S-182 88, Swed.
SOURCE: Journal of Hypertension (2001), 19(6), 1167-1176
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

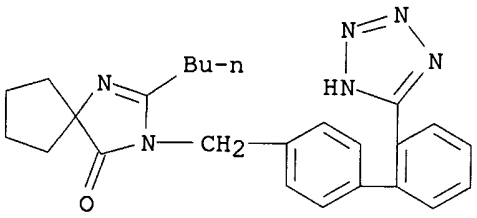
AB We hypothesized that blockade of angiotensin II subtype 1 (AT1) receptors by the AT1-receptor antagonist irbesartan would reduce left ventricular mass (as measured by echocardiog.) more than conventional treatment with a beta blocker. This double-blind study randomized 115 hypertensive men and women with left ventricular hypertrophy to receive either irbesartan 150 mg q.d. or atenolol 50 mg q.d. for 48 wk. If diastolic blood pressure remained above 90 mmHg, doses were doubled, and addnl. medications (hydrochlorothiazide and felodipine) were prescribed as needed.

Echocardiog. was performed at weeks 0, 12, 24 and 48. Baseline mean blood pressure was 162/104 mmHg, and mean left ventricular mass index was 157 g/m2 for men and 133 g/m2 for women. Systolic and diastolic blood pressure redns. were similar in both treatment groups. Both irbesartan (P < 0.001) and atenolol (P < 0.001) progressively reduced left ventricular mass index, e.g. by 26 and 14 g/m2 (16 and 9%), resp., at week 48, with a greater redn. in the irbesartan group (P = 0.024). The proportion of patients who attained a normalized left ventricular mass (i.e. .ltoreq. 131 g/m2 for men and .ltoreq. 100 g/m2 for women) tended to be greater with irbesartan (47 vs. 32%, P = 0.108). Conclusions Left ventricular mass was reduced more in the irbesartan group than in the atenolol group. These results suggest that blocking the action of angiotensin II at AT1-receptors may be an important mechanism, beyond that of lowering blood pressure, in the regulation of left ventricular mass and geometry in patients with **hypertension**.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regression of left ventricular hypertrophy in human **hypertension** with irbesartan)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:179110 CAPLUS
DOCUMENT NUMBER: 135:161974
TITLE: Left ventricular hypertrophy and angiotensin II antagonists
AUTHOR(S): Dahlof, Bjorn
CORPORATE SOURCE: Clinical Experimental Research Laboratory, Sahlgrenska University Hospital, Goteborg, S-416 85, Swed.
SOURCE: American Journal of Hypertension (2001), 14(2), 174-182
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

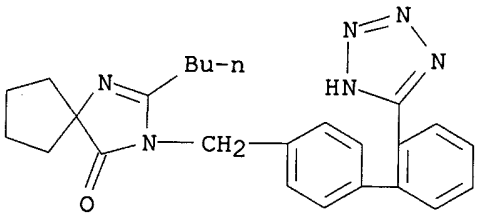
AB A review with 69 refs. Left ventricular hypertrophy in patients with **hypertension** is an important condition. It is assocd. with significant mortality and carries increased risk for developing nonfatal **cardiovascular** complications, including coronary heart **disease**. The pathogenesis of left ventricular hypertrophy is linked to activation of the renin-angiotensin system, with excessive prodn. of angiotensin II believed to be responsible. The therapeutic

benefit of blocking angiotensin II at the receptor with selective angiotensin II antagonists, a relatively new class of antihypertensive agents, is therefore considered for regression of left ventricular hypertrophy. Clin. evidence shows significant efficacy in reversing left ventricular hypertrophy in hypertensive patients after treatment with angiotensin II antagonists. Published data include open-label and randomized studies with losartan treatment for left ventricular hypertrophy, with fewer studies investigating the effects of valsartan, irbesartan, and candesartan.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(left ventricular hypertrophy and angiotensin II antagonists in humans with **hypertension**)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

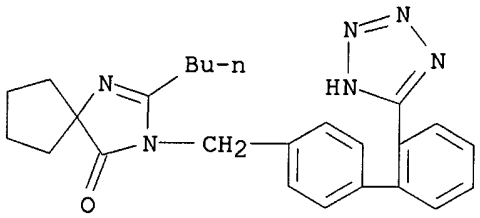
L10 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:876731 CAPLUS
DOCUMENT NUMBER: 134:37023
TITLE: Combinations of CRF antagonists and renin-angiotensin system inhibitors
INVENTOR(S): Fossa, Anthony Andrea
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1059100	A2	20001213	EP 2000-304785	20000606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6387894	B1	20020514	US 2000-587182	20000602

PRIORITY APPLN. INFO.: US 1999-138734P P 19990611
OTHER SOURCE(S): MARPAT 134:37023

AB Compns. and methods are provided for achieving a therapeutic effect including, but not limited to, the treatment of congestive heart failure or **hypertension** in an animal, preferably a mammal including a human subject or a companion animal, using a corticotropin releasing factor (CRF) antagonist and a renin-angiotensin system (RAS) inhibitor.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CRF antagonist therapeutic combination with renin-angiotensin system inhibitor)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:459803 CAPLUS
DOCUMENT NUMBER: 133:52972
TITLE: Irbesartan: an updated review of its use in **cardiovascular** disorders
AUTHOR(S): Markham, Anthony; Spencer, Caroline M.; Jarvis, Blair
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (2000), 59(5), 1187-1206
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

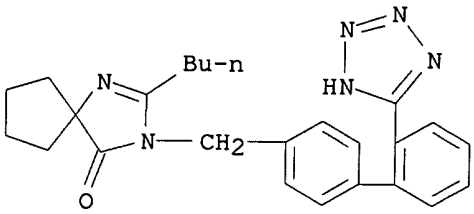
AB A review with 100 refs. Irbesartan interrupts the renin-angiotensin system via selective blockade of the angiotensin II subtype I receptor; the latter being responsible for the pressor related effects of angiotensin II. As treatment for mild to moderate **hypertension**, irbesartan 150 mg/day controlled diastolic BP in 56% of patients according to pooled data from several phase III studies and 77% of patients in a large phase IV study. In comparative trials, irbesartan was significantly more effective than losartan and valsartan as treatment for mild to moderate essential **hypertension** and as effective as enalapril or atenolol. Results from many studies show an additive antihypertensive effect when hydrochlorothiazide is added to irbesartan monotherapy. The drug also induces statistically significant regression of left ventricular mass in patients with **hypertension** and left ventricular hypertrophy, and preliminary evidence suggests it has beneficial hemodynamic effects in patients with heart failure. Irbesartan is very well tolerated, exhibiting an adverse event profile similar to that seen with placebo in comparative trials. In conclusion, although the role of irbesartan as a treatment for heart failure is little clearer than it was 2 yr ago, the place of the drug in the management of **hypertension** is now better established. There is evidence to suggest the drug may have a role as initial therapy for **hypertension**, although formal recommendation in management guidelines will almost certainly not occur until long term morbidity and mortality benefits are established.

IT **138402-11-6**, Irbesartan
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(irbesartan use in **cardiovascular** disorders in humans)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:229720 CAPLUS

DOCUMENT NUMBER: 133:1126

TITLE: Blockade of angiotensin II type 1 receptors: effect on carotid and radial artery structure and function in hypertensive humans

AUTHOR(S): Benetos, A.; Gautier, S.; Lafleche, A.; Topouchian, J.; Frangin, G.; Girerd, X.; Sissmann, J.; Safar, M. E.

CORPORATE SOURCE: Department of Internal Medicine and INSERM (U337), Broussais Hospital, Paris, F-75674, Fr.

SOURCE: Journal of Vascular Research (2000), 37(1), 8-15
CODEN: JVREE9; ISSN: 1018-1172

PUBLISHER: S. Karger AG

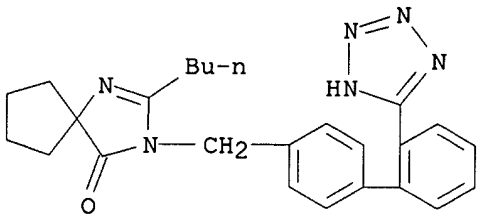
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Converting-enzyme inhibition reduces **cardiovascular** hypertrophy in hypertensive subjects. Whether the blockade of angiotensin II type 1 (AT1) receptors reduces arterial hypertrophy has never been investigated. In a double-blind study vs. placebo in subjects with essential **hypertension**, the effect of the AT1 blocker irbesartan (150 mg/day for 8 wk) on blood pressure, wall thickness, diam. and stiffness of the common carotid and radial arteries was studied, using echo-tracking techniques of high resoln. With irbesartan, mean blood pressure decreased significantly and proportionally to the baseline levels of active renin, and angiotensin I and II. There was a significant decrease in radial artery wall thickness. The percent change from baseline (.+-. SEM) was -10.51 .+-. 3.42 vs. 6.18 .+-. 4.77. · There was no significant change in diam. or distensibility. This effect was correlated neither to blood pressure changes nor to hormonal baseline levels of the renin-angiotensin system. Carotid wall thickness and diam. were unchanged. Thus a 2-mo treatment with an AT1 antagonist significantly reduced radial but not carotid artery wall thickness. Blood pressure redn. could be explained on the basis of circulating renin-angiotensin activity. On the contrary, radial artery wall thickness redn. was independent of the baseline circulating renin-angiotensin activity and was not correlated with the effects of AT1 blockade on blood pressure, thus implying the involvement of local hemodynamic and/or cellular mechanisms.

09720017

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blockade of angiotensin II type 1 receptors: effect on carotid and radial artery structure and function in hypertensive humans)
RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

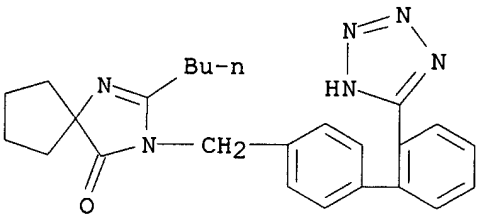
L10 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:225144 CAPLUS
DOCUMENT NUMBER: 132:231405
TITLE: The benefits of angiotensin II receptor antagonists in high-risk hypertensive patients with diabetes
AUTHOR(S): Porush, J. G.
CORPORATE SOURCE: SUNY Health Science Center, Brookdale University Hospital and Medical Center, Brooklyn, NY, 11212, USA
SOURCE: European Heart Journal Supplements (2000), 2(Suppl. B), B22-B27
CODEN: EHJSFT; ISSN: 1520-765X
PUBLISHER: W. B. Saunders Co. Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 35 refs. The coexistence of diabetes and **hypertension** portend increased macrovascular and microvascular complications, with an increased risk for **cardiovascular** death, including myocardial infarction, congestive heart failure, stroke and peripheral vascular **disease**. Several studies have reported that stringent blood pressure control reduces the risk of **cardiovascular** events and diabetes-related mortality. Addnl. benefits beyond those incurred from lowering blood pressure have been noted with the use of angiotensin-converting enzyme (ACE) inhibitors in high-risk groups. These effects are possibly due to the benefits of blocking the renin-angiotensin system (RAS). ACE inhibitors have been shown to slow the progression of renal **disease** by slowing the rate of decline of glomerular filtration and reducing proteinuria in patients with type 1 diabetes, and by slowing the progression of retinopathy in normotensive diabetics. Preliminary data suggest that a new class of antihypertensives, the angiotensin II receptor antagonists (AIIRAs), may reduce **cardiovascular** risk to at least the same extent as ACE inhibitors. The ACCRA irbesartan has achieved superiority within its class because of the extent and duration of RAS blockade and antihypertensive efficacy. In animal models of renal **disease**, irbesartan was found to produce significant dose-related redns. in glomerular injury, prevent the development of proteinuria and

glomerulosclerosis, and normalize glomerular capillary pressure. The Program for Irbesartan Mortality and Morbidity Evaluations (PRIME) is an important research program composed of two ongoing trials. The Irbesartan Diabetic Nephropathy Trial (IDNT) will assess the effects of irbesartan, the calcium channel blocker amlodipine or placebo (usual care) on **cardiovascular** morbidity and mortality and the progression of renal **disease** in high-risk hypertensive patients with type 2 diabetes and proteinuria. The IRbesartan MicroAlbuminuria (IRMA) II trial will assess the effects of irbesartan or placebo (usual care) on the progression of microalbuminuria to overt nephropathy in hypertensive patients with type 2 diabetes, microalbuminuria and normal renal function. The results of these trials will be used to evaluate the **cardiovascular** and renal benefits of irbesartan in high-risk patients with **hypertension** and type 2 diabetes at both early and advanced stages of renal **disease**.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benefits of angiotensin II receptor antagonists and ACE inhibitors in high-risk hypertensive humans with diabetes)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:225141 CAPLUS
DOCUMENT NUMBER: 132:231402
TITLE: Blood pressure control: a review on irbesartan
AUTHOR(S): Waeber, B.
CORPORATE SOURCE: Division of Pathophysiology and Medical Teaching, University Hospital, Lausanne, CH-1011, Switz.
SOURCE: European Heart Journal Supplements (2000), 2(Suppl. B), B2-B7
CODEN: EHJSFT; ISSN: 1520-765X
PUBLISHER: W. B. Saunders Co. Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

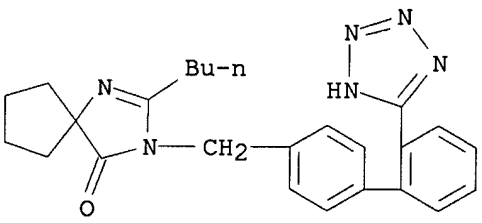
AB A review with 37 refs. Despite the substantial evidence documenting that **hypertension** increases the risk of **cardiovascular disease** events, the extent of control of blood pressure remains poor worldwide. The availability of numerous antihypertensive agents in various classes has not ameliorated the situation. Though difficult to assess definitively, the reasons for this poor control may partly be related to the dose-related increase in side-effects obsd. with most antihypertensive agents, and to the need for simple, tolerable combination

therapy to control blood pressure in a wide range of patients. The availability of the angiotensin II receptor antagonists (AIIRAs), and recently of fixed-dose combination therapy with ACCRAs and thiazide diuretics, may have the potential to improve the poor control rates in **hypertension**. Irbesartan is a member of the ACCRA class that has very attractive pharmacokinetic and clin. features. Among these features are dose-related efficacy with no dose-response with respect to adverse events, as well as effective and long-lasting blockade of angiotensin II. The recently available fixed-dose combination of irbesartan/hydrochlorothiazide extends the pos. results obsd. with irbesartan monotherapy by offering blood pressure control rates in the majority of patients. This treatment leads to no significant difference in adverse events compared with placebo or irbesartan monotherapy.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irbesartan for control of blood pressure in humans)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:807176 CAPLUS

DOCUMENT NUMBER: 132:132083

TITLE: The angiotensin AT1 receptor antagonist irbesartan has near-peptide affinity and potently blocks receptor signaling

AUTHOR(S): Hines, J.; Fluharty, S. J.; Sakai, R. R.

CORPORATE SOURCE: Department of Pharmacology, University of Pennsylvania, Philadelphia, PA, USA

SOURCE: European Journal of Pharmacology (1999), 384(1), 81-89
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

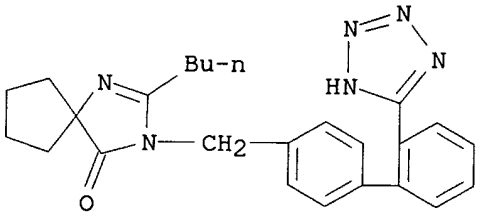
AB The angiotensin II type 1 (AT1) receptor plays a pivotal role in the regulation of blood pressure and electrolyte balance, and is involved in the control of specific ingestive behaviors. Irbesartan (SR 47436/BMS 186295) is a recently developed angiotensin AT1 receptor antagonist, chem. described as 2-butyl-3-([2'-{1H-tetrazol-5-yl}biphenyl-4-yl]methyl)-1,3-diazaspiro (4,4)non-1-en-4-one. Irbesartan displays higher affinity for its target receptor than other similar antagonists. In radioligand binding assays performed on membranes from WB-Fischer 344 (WB) rat liver epithelial cells, irbesartan was able to displace [125I]angiotensin II with a Ki of 4.05 nM as compared to losartan (DuP 753) and tasosartan (WAY

126756), which had Ki values of 25.2 nM and 46.6 nM, resp. Similarly, in functional assays, irbesartan exhibited the highest functional potency to block angiotensin II-induced inositol trisphosphate (IP3) turnover. The improved affinity of irbesartan for the angiotensin AT1 receptor does not coincide with a concomitant increase in affinity for the angiotensin AT2 receptor, as irbesartan and losartan exhibited the same low potency to displace [125I]angiotensin II in radioligand binding assays performed on membranes from PC-12w cells. In binding assays performed on peripheral tissues in rat, irbesartan bound to the angiotensin AT1 receptor expressed in liver, adrenal, kidney and pituitary with an overall affinity closely approaching that of the high affinity peptidic antagonist [Sar1, Ile8]angiotensin II. Due to the higher affinity of irbesartan over other similar antagonists for the angiotensin AT1 receptor in many tissues and its greater potency to block receptor activation, irbesartan may be quite useful in the study of the angiotensin AT1 receptor and its role in controlling ingestive behaviors and, furthermore, shows great potential to improve the treatment of **hypertension** and other **cardiovascular disease** states.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin AT1 receptor antagonist irbesartan has near-peptide affinity and potently blocks receptor signaling)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:708612 CAPLUS
DOCUMENT NUMBER: 131:327536
TITLE: Pharmaceutical compositions containing in combination an arginine-vasopressin V1a antagonist and an angiotensin II AT1 receptor antagonist
INVENTOR(S): Nisato, Dino
PATENT ASSIGNEE(S): Sanofi-Synthelabo, Fr.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9955340	A1	19991104	WO 1999-FR959	19990422

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

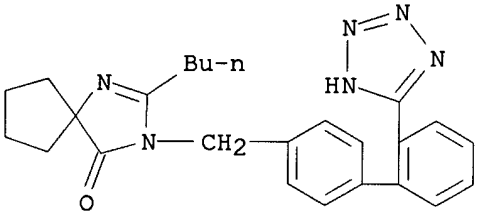
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2778103	A1	19991105	FR 1998-5591	19980429
AU 9934259	A1	19991116	AU 1999-34259	19990422
PRIORITY APPLN. INFO.:			FR 1998-5591	19980429
			WO 1999-FR959	19990422

AB Pharmaceutical compns. are provided which contain a combination of a arginine-vasopressin V1a antagonist and an angiotensin II AT1 receptor antagonist. The compns. are useful for treating e.g. cardiac deficiency, high blood pressure and nephropathy.

IT **138402-11-6**, Irbesartan **248250-84-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arginine-vasopressin V1a antagonist-angiotensin II AT1 receptor antagonist combination pharmaceutical compns. and therapeutic use)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



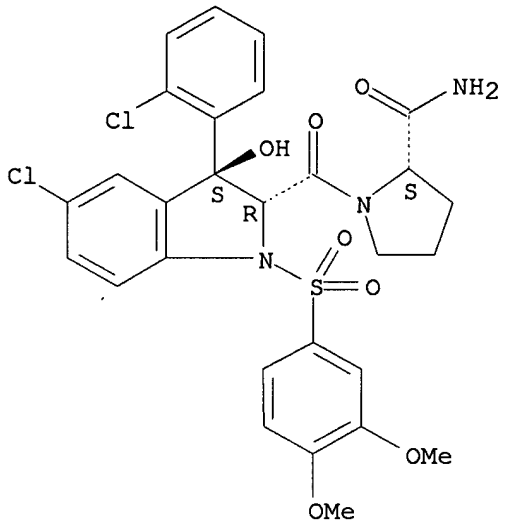
RN 248250-84-2 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[[(2R,3S)-5-chloro-3-(2-chlorophenyl)-1-[(3,4-dimethoxyphenyl)sulfonyl]-2,3-dihydro-3-hydroxy-1H-indol-2-yl]carbonyl]-, (2S)-, mixt. with 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (9CI) (CA INDEX NAME)

CM 1

CRN 150375-75-0
CMF C28 H27 Cl2 N3 O7 S

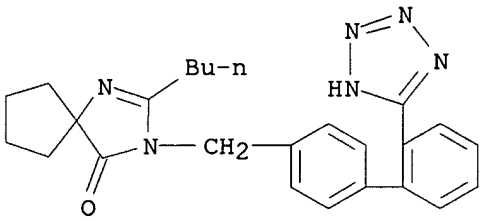
Absolute stereochemistry. Rotation (-).

09720017



CM 2

CRN 138402-11-6
CMF C25 H28 N6 O



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:168574 CAPLUS
DOCUMENT NUMBER: 128:252389
TITLE: Human pharmacokinetic/pharmacodynamic profile of irbesartan: a new potent angiotensin II receptor antagonist
AUTHOR(S): Ruilope, Luis
CORPORATE SOURCE: Hypertension Unit, Hospital 12 de Octubre, Madrid, E-28041, Spain
SOURCE: Journal of Hypertension (1997), 15(Suppl. 7), S15-S20
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Rapid Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

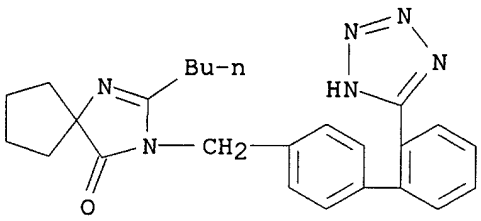
AB A review, with 35 refs. Inhibition of the renin-angiotensin system has been the focus of considerable research as the enzymic pathway resulting in the prodn. of angiotensin II is implicated in the development of **hypertension** and **cardiovascular disease**.
Blocking the renin-angiotensin system with angiotensin converting enzyme (ACE) inhibitors is an effective blood pressure control measure, but is

less than ideal due to incomplete blockade and the effects of concomitant blockade of kinase II. Angiotensin II receptor antagonists block the renin-angiotensin system at the receptor level, and thus impede the system regardless of the pathway responsible for the formation of ACE. Irbesartan is a new, unique angiotensin II receptor antagonist with favorable pharmacokinetic/pharmacodynamic properties that are close to ideal for an antihypertensive agent. Irbesartan is a specific AT1 receptor antagonist with rapid oral bioavailability (peak plasma concns. occurring at 1.5-2 h after administration) and a long half-life (11-15 h) that provides 24-h blood pressure control with a single daily dose. The maximal blood pressure fall occurs between 3 and 6 h after the dose. Unlike other angiotensin II receptor antagonists, irbesartan is relatively unaffected by food or drugs. The pharmacokinetic/pharmacodynamic properties of irbesartan have been demonstrated to provide superior blood pressure control and tolerability in all classes of **hypertension** and patient populations.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(human pharmacokinetic/pharmacodynamic profile of irbesartan as angiotensin II receptor antagonist)

RN 138402-11-6 CAPLUS

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:168548 CAPLUS
DOCUMENT NUMBER: 126:152804
TITLE: Spironolactone or other epoxy-free spirolactone-type aldosterone receptor antagonist in combination with angiotensin II antagonist for treatment of circulatory and **cardiovascular** disorders, including congestive heart failure
INVENTOR(S): Maclaughlan, Todd E.; Schuh, Joseph R.
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Maclaughlan, Todd E.; Schuh, Joseph R.
SOURCE: PCT Int. Appl., 210 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640258	A2	19961219	WO 1996-US9342	19960605
WO 9640258	A3	19970123		

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA

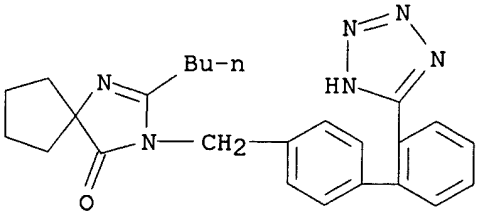
CA 2224222	AA	19961219	CA 1996-2224222	19960605
AU 9661580	A1	19961230	AU 1996-61580	19960605
EP 831911	A2	19980401	EP 1996-919173	19960605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1192696	A	19980909	CN 1996-196086	19960605
BR 9608505	A	19990706	BR 1996-8505	19960605
JP 11509838	T2	19990831	JP 1996-501683	19960605
AT 216261	E	20020515	AT 1996-919173	19960605
PRIORITY APPLN. INFO.:			US 1995-486089 A	19950607
			WO 1996-US9342 W	19960605

OTHER SOURCE(S): MARPAT 126:152804

AB A combination therapy is disclosed which comprises a therapeutically-effective amt. of an epoxy-free spirolactone-type aldosterone receptor antagonist and a therapeutically-effective amt. of an angiotensin II receptor antagonist for treatment of circulatory disorders, including **cardiovascular** disorders, e.g. **hypertension** and congestive heart failure. Preferred angiotensin II receptor antagonists are those compds. having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. A preferred epoxy-free spirolactone-type aldosterone receptor antagonist is spironolactone. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist spironolactone.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(spironolactone or other epoxy-free spirolactone-type aldosterone receptor antagonist in combination with angiotensin II antagonist for treatment of circulatory and **cardiovascular** disorders, including congestive heart failure)

RN 138402-11-6 CAPLUS
CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L10 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:168547 CAPLUS
DOCUMENT NUMBER: 126:152803
TITLE: Epoxy-steroidal aldosterone antagonist and angiotensin II antagonist combination therapy for treatment of

09720017

cardiovascular disorders, including congestive heart failure

INVENTOR(S): Alexander, John C.; Schuh, Joseph R.; Gorczynski, Richard J.

PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Alexander, John C.; Schuh, Joseph R.; Gorczynski, Richard J.

SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640257	A1	19961219	WO 1996-US9335	19960605
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2224079	AA	19961219	CA 1996-2224079	19960605
AU 9661577	A1	19961230	AU 1996-61577	19960605
AU 725689	B2	20001019		
EP 831910	A1	19980401	EP 1996-919170	19960605
EP 831910	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1192697	A	19980909	CN 1996-196155	19960605
BR 9609066	A	19990126	BR 1996-9066	19960605
JP 11507627	T2	19990706	JP 1996-501678	19960605
RU 2166330	C2	20010510	RU 1998-100250	19960605
AT 209047	E	20011215	AT 1996-919170	19960605
ES 2167571	T3	20020516	ES 1996-919170	19960605
NO 9705741	A	19980129	NO 1997-5741	19971205

PRIORITY APPLN. INFO.: US 1995-486456 A 19950607
WO 1996-US9335 W 19960605

OTHER SOURCE(S): MARPAT 126:152803

AB A combination therapy comprising a therapeutically-effective amt. of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amt. of an angiotensin II receptor antagonist is described for treatment of circulatory disorders, including **cardiovascular** disorders, e.g. **hypertension** and congestive heart failure. Preferred angiotensin II receptor antagonists are those compds. having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compds. characterized by the presence of 9.alpha.,11.alpha.-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.

IT **138402-11-6**, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(epoxy-steroidal aldosterone antagonist and angiotensin II antagonist combination therapy for treatment of **cardiovascular** disorders, including congestive heart failure)

RN 138402-11-6 CAPLUS

09720017

CN 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)